Slides for public observers – no ACIC

Lead team presentation
Midostaurin for untreated acute myeloid leukaemia [ID894] – STA

1st Appraisal Committee meeting

Committee C

Lead team:

Clinical: Derek Ward and David Chandler
Cost: Stephen O'Brien

ERG: CRD and CHE, University of York

NICE technical team: Kirsty Pitt and Sally Doss

9 November 2017

Key issues – clinical effectiveness

- Is the treatment schedule used in RATIFY representative of clinical practice in the NHS?
- Is the population in the trial relevant to clinical practice in the NHS?
- Will midostaurin be used for older patients (over 60 / over 70)?
- Is midostaurin clinically effective?
- Are the adverse effects of midostaurin acceptable compared with standard of care?
- Is there uncertainty in the results because subsequent therapies were not recorded in the trial (including subsequent chemotherapy and stem cell transplant data)?
- Does the company's phase II trial provide evidence that midostaurin is effective across different age groups?

Disease background

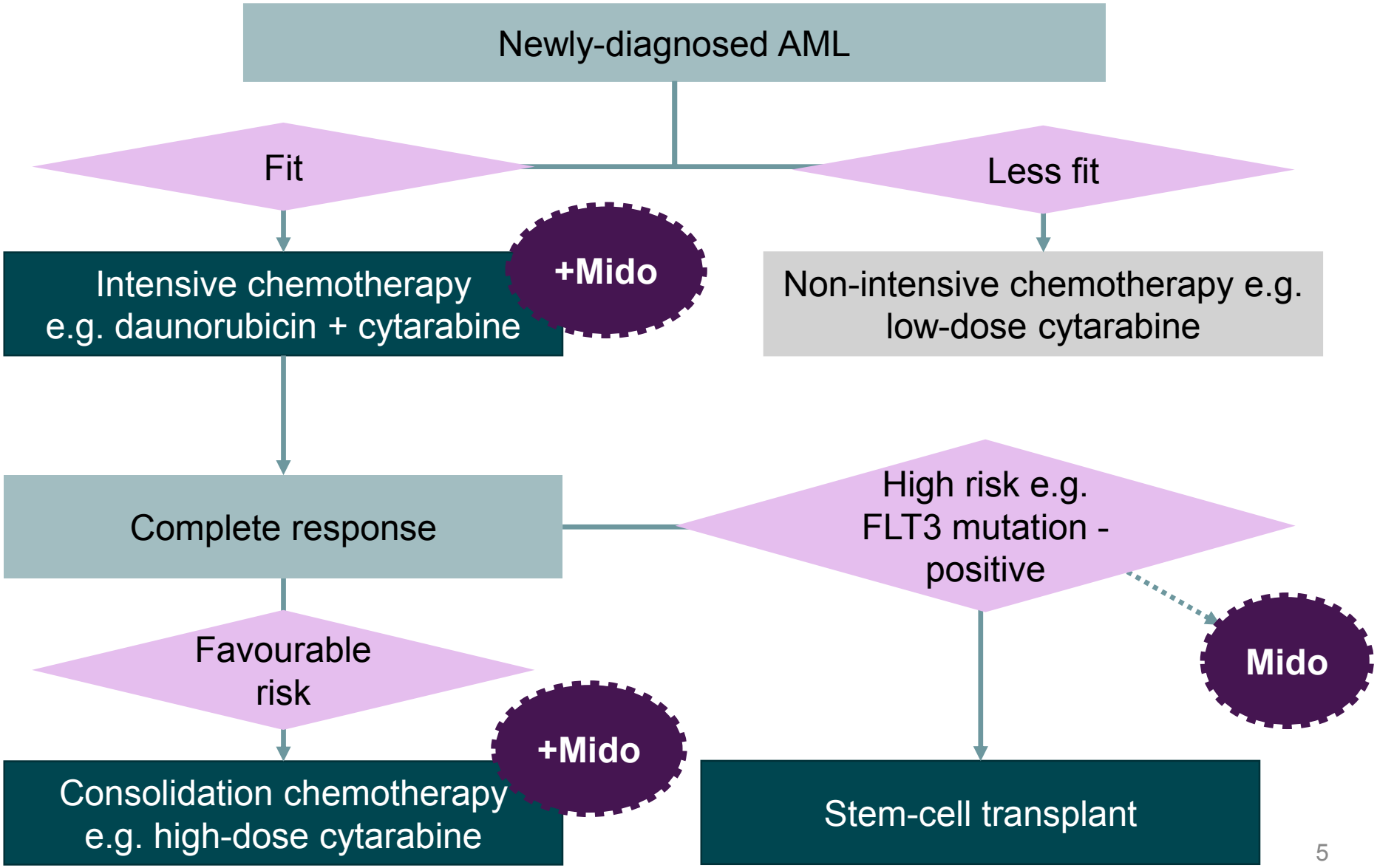
- Acute myeloid leukaemia has one of the lowest survival rates among leukaemias
- 2,590 new cases in England in 2014
- Rarely diagnosed before age of 40 – 55% of patients were 70 or older in 2011-2013
- More common in men than women
- Approximately 30% have FLT3 mutation-positive disease
- Approximately 85% receive systemic therapy, and 75% of these receive intensive chemotherapy

Midostaurin (Rydapt)
Novartis

UK marketing authorisation	Indicated in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive
Administration	Oral therapy
Mechanism of action	Multi-targeted kinase inhibitor, found to inhibit FLT3 and other receptor tyrosine kinases.
Dosage	50 mg twice daily (2 x 25 mg soft gel capsules) on days 8–21 of induction and consolidation chemotherapy cycles, and then twice daily as single-agent therapy for up to 12 months
Cost	List price: [redacted] for 56 capsules*

*Pack size changed from 112 to 56 tablets Nov 2017. No effect on cost-effectiveness analyses.

Current treatment pathway



Decision problem

	Final scope issued by NICE	Company submission
Population	People with newly diagnosed, FLT3 mutation-positive acute myeloid leukaemia	People with newly diagnosed, FLT3 mutation-positive acute myeloid leukaemia
Intervention	Midostaurin in combination with standard induction and consolidation chemotherapy followed by single-agent maintenance therapy	Midostaurin in combination with established chemotherapy followed by midostaurin monotherapy
Comparator	Established clinical management without midostaurin	Same as final scope issued by NICE
Outcomes	The outcome measures to be considered include: • overall survival • event-free survival • disease-free survival • adverse effects of treatment • health-related quality of life	Same as final scope issued by NICE except for omission of health-related quality of life which was not assessed in the clinical trials

Related NICE guidance

TA399

Azacitidine is not recommended, within its marketing authorisation, for treating acute myeloid leukaemia with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant.

TA218

Azacitidine is recommended as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification, and if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme.

Comments from professional groups and NHS England

- Professional groups
  - FLT-3 mutation testing done at diagnosis but results may not be available when therapy is initiated
  - 20-25% patients have FLT3-ITD mutation – increased relapse rate and poorer overall survival. 5-8% have FLT3-TKD mutation – better prognosis
  - Some differences between numbers of chemotherapy cycles and length of induction treatment in RATIFY and NHS practice

- NHS England
  - For each month of maintenance midostaurin treatment, hospital trusts would charge NHS England a monthly oral chemotherapy HRG tariff (£120) – no charge currently as no active maintenance therapy
  - Cost of cytotoxic chemotherapy should be taken from eMIT, not BNF, although would make little difference to ICER
  - No UK patients in RATIFY trial – issue for generalisability

Patient perspective (1)
Living with acute myeloid leukaemia (AML)
(Leukaemia CARE submission)

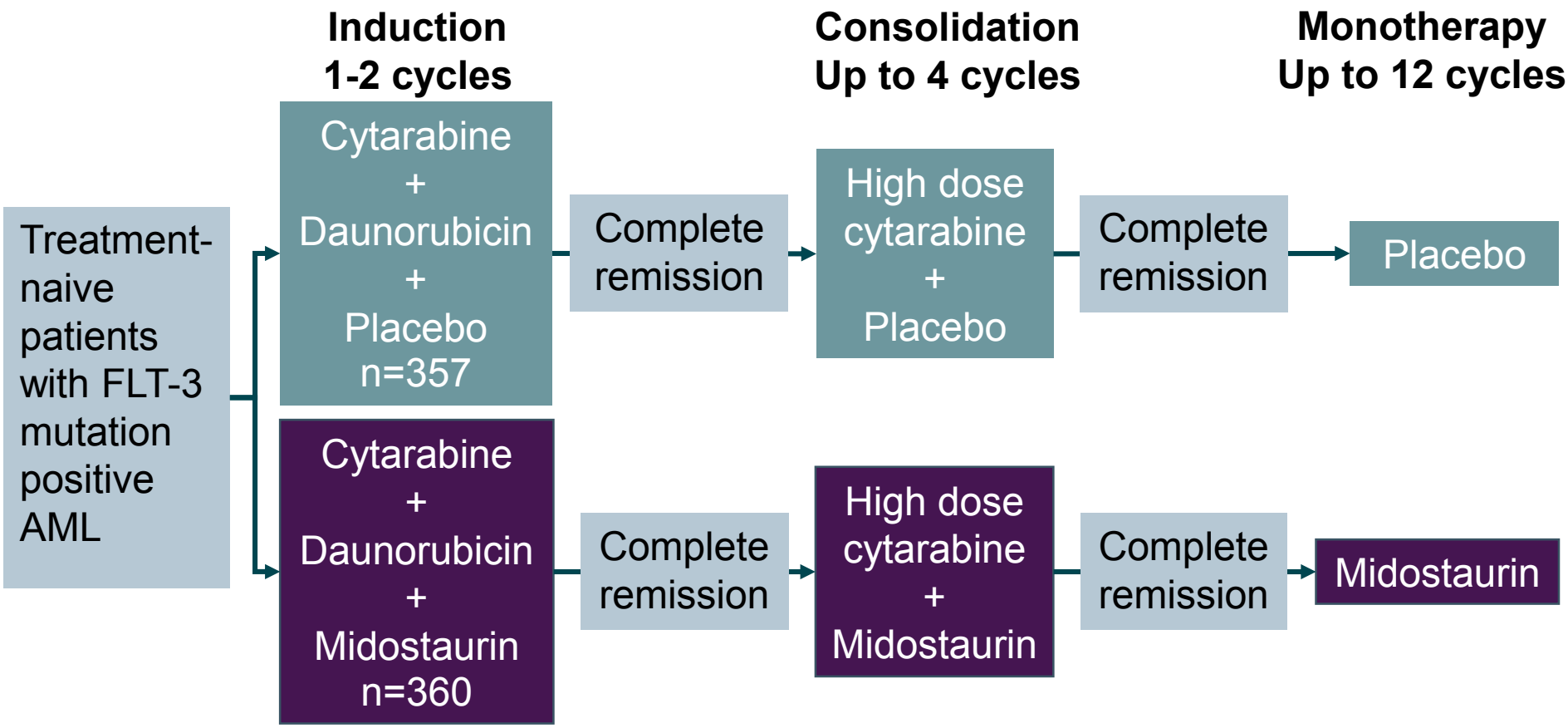
- Rapidly progressing form of leukaemia
- 53% diagnosed following emergency admission
- Prognosis is poor >50% of leukaemia deaths are AML
- Symptoms include: *Fatigue, feeling weak, breathlessness, frequent infections, memory loss, itchy skin, nausea/vomiting, sleeping problems, bone pain, weight loss and muscle pain*
- Following diagnosis patients report:
  - *A huge emotional impact, with feelings of disbelief, denial, anger and depression.*
  - *Daily routines and moving around also affected: Including cooking, cleaning, ability to work and to continue in education*
- Also causes emotional strain on carers and family members
- Improvement in patient prognosis can also have a wider impact on the lives of those around them

Patient perspective (2)
What patients want from treatments

- A remission and response
- Longer survival
- Improved quality of life
- Reduced and tolerable side-effects
- Improved blood counts
- Reduced impact on family and carers
- Midostaurin is an oral treatment

Company's clinical evidence

RATIFY trial: midostaurin vs placebo (N=717)



- Multi-centre, phase 3, randomised 1:1, double-blind, placebo-controlled trial
- Midostaurin in combination with standard chemotherapy
- Inclusion criteria: aged ≥18 and <60 years

Baseline characteristics in RATIFY (1)

Full population

Characteristic	Midostaurin (N = 360)	Placebo (N = 357)	Total (N = 717)
Age, years			
Mean (SD)	44.9 (10.4)	45.5 (10.8)	45.2 (10.6)
Median (range)	47.0 (19–59)	48.0 (18–60)	47.0 (18–60)
Male, n (%)	174 (48.3)	145 (40.6)	319 (44.5)
BSA, mean (SD) m^2	2.0 (0.29)	1.9 (0.28)	1.9 (0.28)
ECOG/Zubrod Performance Status, n (%)			
0	164 (45.6)	142 (39.8)	306 (42.7)
1	159 (44.2)	168 (47.1)	327 (45.6)
2	29 (8.1)	36 (10.1)	65 (9.1)
3	6 (1.7)	9 (2.5)	15 (2.1)
4	2 (0.6)	2 (0.6)	4 (0.6)

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group

Baseline characteristics in RATIFY (2)

Full population

Characteristic	Midostaurin (N = 360)	Placebo (N = 357)	Total (N = 717)
Race, n (%)			
White	147 (40.8)	128 (35.9)	275 (38.4)
Black or African American	8 (2.2)	9 (2.5)	17 (2.4)
Asian	8 (2.2)	5 (1.4)	13 (1.8)
American Indian or Alaskan native	0	1 (0.3)	1 (0.1)
Not reported	1 (0.3)	2 (0.6)	3 (0.4)
More than one race	2 (0.6)	1 (0.3)	3 (0.4)
Unknown	194 (53.9)	211 (59.1)	405 (56.5)
Region, n (%)			
North America	121 (33.6)	115 (32.2)	236 (32.9)
Non-North America	239 (66.4)	242 (67.8)	481 (67.1)
FLT3 mutation status, n (%)			
Tyrosine kinase domain (TKD)	83 (23.1)	80 (22.4)	163 (22.7)
Internal tandem duplication (ITD) (includes patients with both TKD and ITD)	276 (76.7)	274 (76.8)	550 (76.7)
ITD Allelic ratio <0.7	164 (45.6)	165 (46.2)	329 (45.9)
ITD Allelic ratio ≥ 0.7	112 (31.1)	109 (30.5)	221 (30.8)
No FLT3 gene mutation	1 (0.3)	3 (0.8)	4 (0.6)

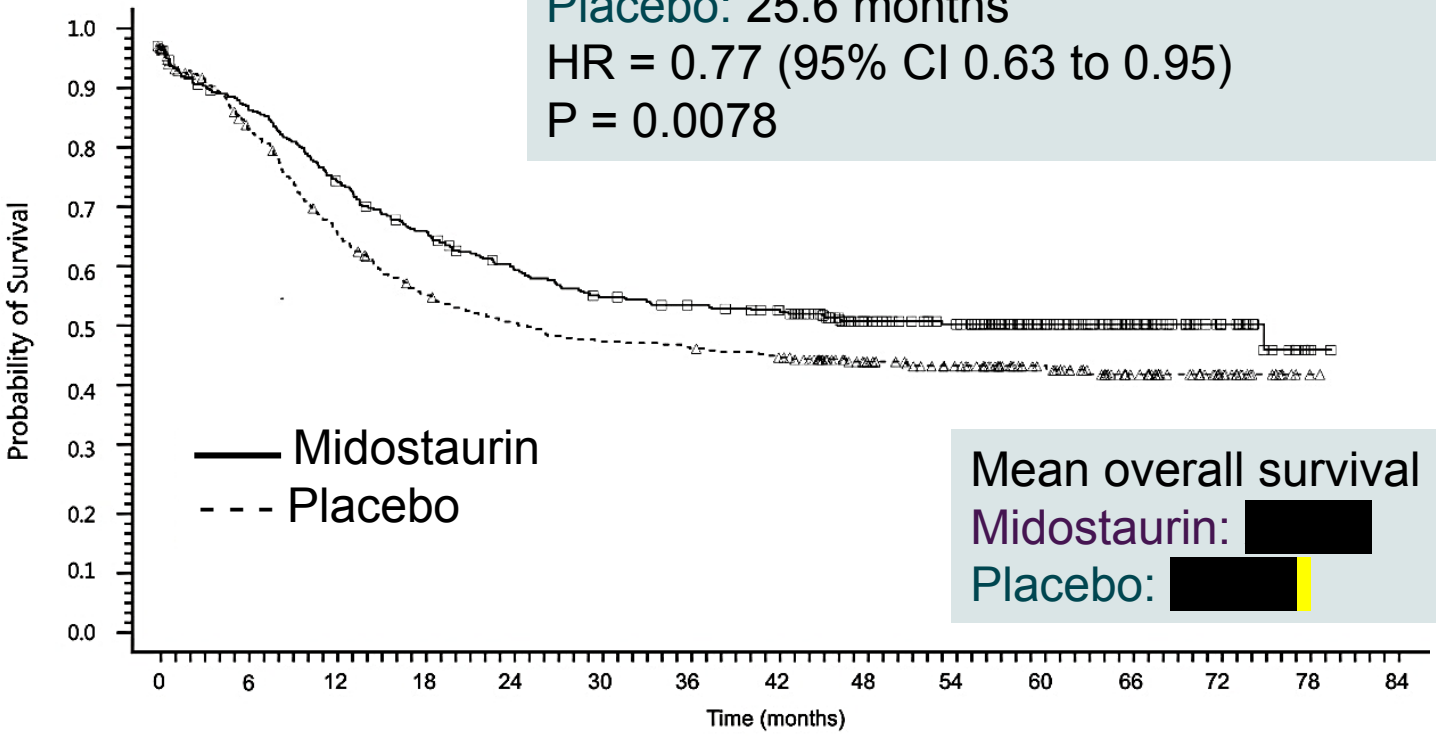
ERG comments on RATIFY trial

Area	ERG comments
Study population	Restricted to people aged 18 to 60 years (mean age 45.2), while in NHS clinical practice, a significant proportion (>60%) of the population of patients with acute myeloid leukaemia to be treated in the UK would be over 60.
Other treatments	Stem cell transplant was not mandated in trial protocol. After treatment discontinuation, patients received either second-line treatment or stem cell transplant ➢ Patient outcomes will be influenced by these subsequent therapies, but they were not recorded as part of the trial ➢ If subsequent therapies received by patients in RATIFY are different to NHS practice, possible that overall survival gains in RATIFY may not be realised in practice
Trial design	Treatment phases of trial similar to expected UK clinical practice ➢ However in practice, patients who do not achieve complete remission after first induction cycle would be given a different chemotherapy for the second cycle

Overall survival – 2015 datacut

Full trial population, non-censored at time of SCT

Median overall survival
Midostaurin: 74.7 months
Placebo: 25.6 months
HR = 0.77 (95% CI 0.63 to 0.95)
P = 0.0078



Mean overall survival
Midostaurin: [redacted]
Placebo: [redacted]

No. of patients still at risk

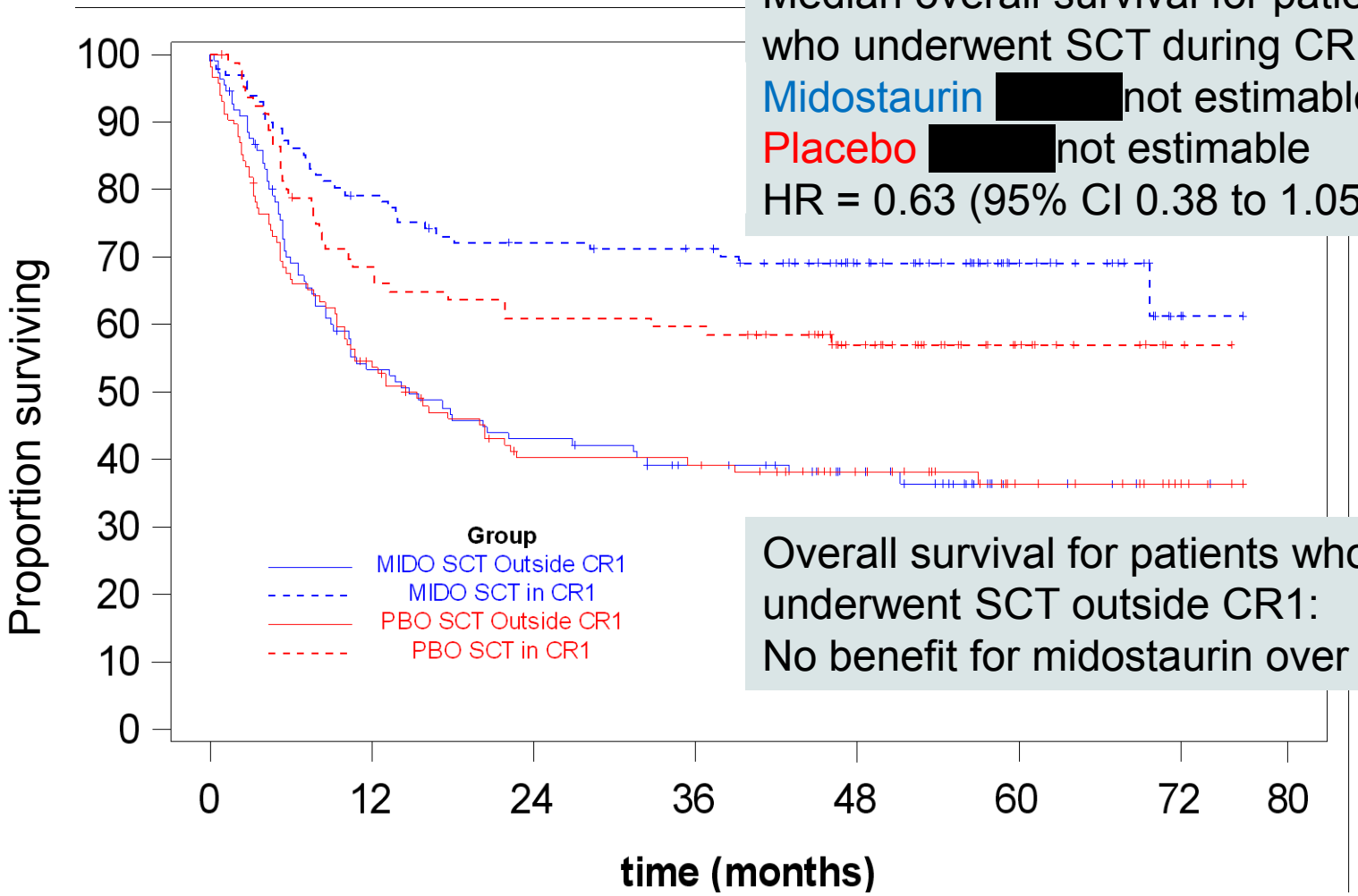
Midostaurin	360	314	269	234	208	189	181	174	133	120	77	50	22	1	0
Placebo	357	284	221	179	163	152	148	141	110	95	71	45	20	1	0

Logrank test and Cox regression model stratified for the FLT3 mutation strata used in the randomization.

SCT, stem cell transplantation; HR, hazard ratio; CI, confidence intervals

Overall survival – 2015 datacut

Patients who underwent stem cell transplantation



Median overall survival for patients who underwent SCT during CR1

Midostaurin [redacted] not estimable

Placebo [redacted] not estimable

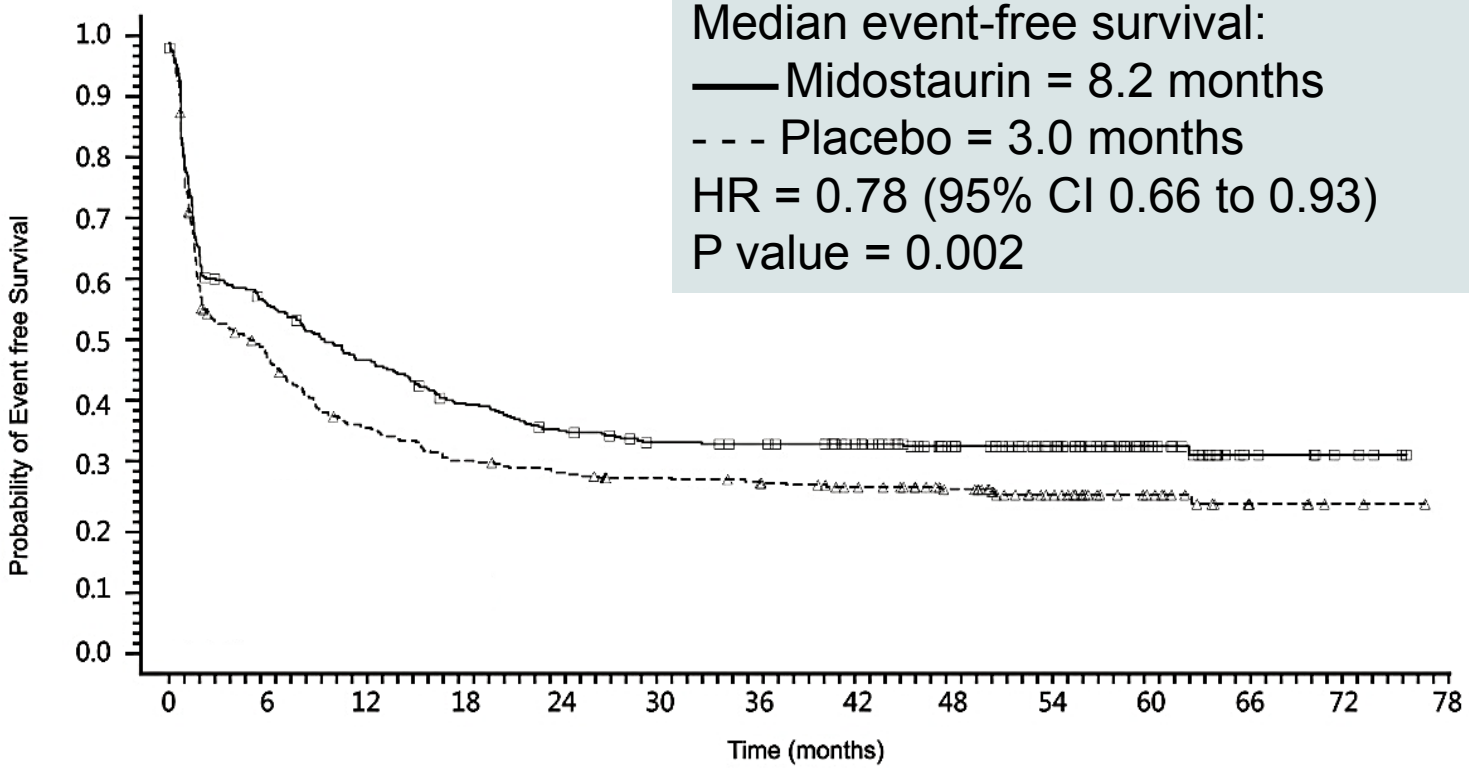
HR = 0.63 (95% CI 0.38 to 1.05)

Overall survival for patients who underwent SCT outside CR1:
No benefit for midostaurin over placebo

SCT, stem cell transplantation; CR1, first complete remission; HR, hazard ratio; CI, confidence intervals

Event-free survival – 2015 datacut

Non-censored at time of stem cell transplant



Median event-free survival:
——Midostaurin = 8.2 months
- - - Placebo = 3.0 months
HR = 0.78 (95% CI 0.66 to 0.93)
P value = 0.002

No. of patients still at risk

Midostaurin	360	190	153	124	106	95	92	83	65	51	27	9	4	0
Placebo	357	153	106	86	78	73	70	60	49	32	18	8	2	0

Logrank test and Coxregression model stratified for the FLT3 mutation strata used in the randomization.

Adverse effects (1)

- Summary of key adverse events reported from the RATIFY trial

	Grade 3/4 AEs suspected be related to treatment	SAEs	Grade 3/4 infections	Withdrawal due to grade 3/4 AEs	Death within 30 days of starting treatment	Deaths at any time
Placebo (N=335)	[redacted]	163 (48.7%)	[redacted]	15 (4.5%)	21 (6.3%)	[redacted]
Midostaurin (N=345)	[redacted]	162 (47%)	[redacted]	21 (6.1%)	15 (4.3%)	[redacted]

Key: AEs, adverse events; SAEs, serious adverse events; SCT, stem cell transplant

Adverse effects (2)

Grade 3/4 treatment-related AEs reported in ≥5% of patients receiving midostaurin across the randomised groups

System organ class AEs	Midostaurin (N=345)	Placebo (N=335)
Non-haematological grade 3/4 AEs in ≥5% of patients in either group, n (%)		
Diarrhoea	[redacted]	[redacted]
Dermatitis exfoliative	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]
Device-related infection	[redacted]	[redacted]
Haematological grade 3/4 AEs in ≥5% of patients in either group, n (%)		
Thrombocytopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]

Dermatitis exfoliative occurred more frequently in midostaurin group – 4 patients in midostaurin group discontinued treatment due to this adverse effect

Company's additional evidence (1)

Submitted after ERG report received

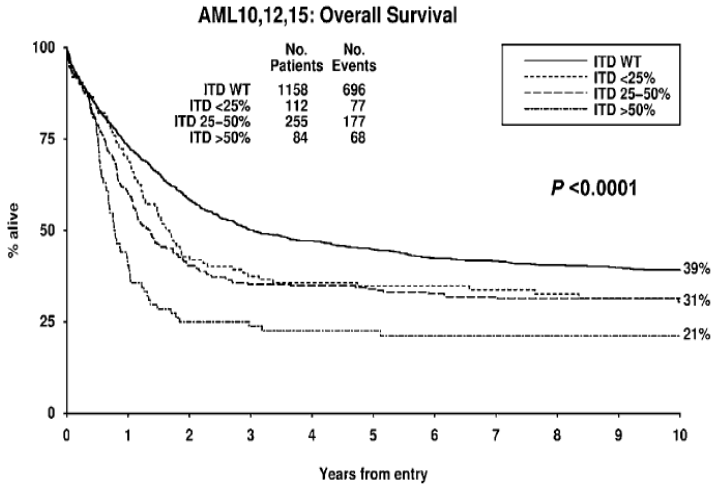
- After receiving the ERG report, company submitted additional evidence about the efficacy of midostaurin in patients over 60

1 Biology of FLT3-positive AML is the same regardless of age group, unlike patients with AML as a whole – therefore patients in target population will not have different prognosis based on age

2 Prognosis of patients with FLT3-positive AML is similarly poor across age groups – comparison of 2 cohorts

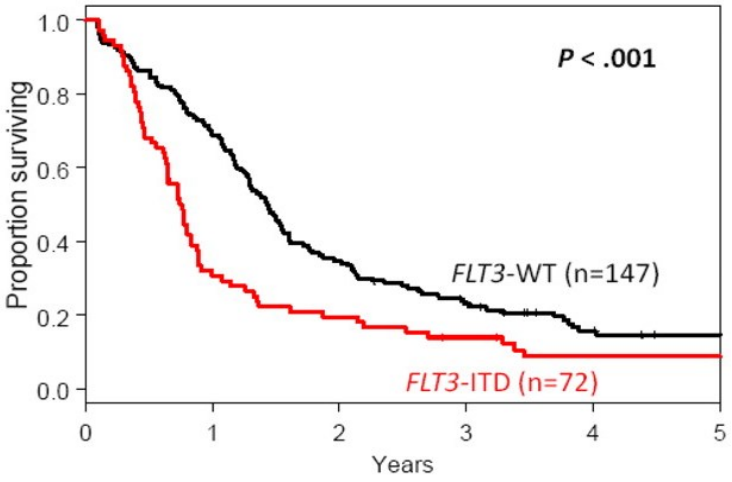
Patients ≤60 years

Linch, Hills & Brunett 2014



Patients >60 years

Whitman, Maharry & Radmacher 2010



Company's additional evidence (2)

Submitted after ERG report received

3 Changes in clinical practice mean that age alone does not determine eligibility for chemotherapy – National Comprehensive Cancer Network guidelines and European Leukemia Network model

- company argues this has led to improved survival rates in the older population

4 Phase 2 study in original submission showed midostaurin is effective in patients over 60 – expanded cohort results below

Results of open label, single-arm phase 2 study of midostaurin in FLT3-positive AML in patients age 18-70 (N=284, 32% ≥60)

Outcome	Patients <60	Patients ≥60	P value
Overall response	76%	76%	0.81
Death	4%	10%	Not reported
Cumulative incidence of relapse and death after transplant	13%	16%	0.41
Median overall survival	26 months	23 months	0.15

Company's additional evidence (3)

Submitted after ERG report received

5 Comparing phase 2 trial data with propensity score-matched historical controls shows efficacy of midostaurin in patients over 60

- Historical controls selected from 5 clinical trials of patients with AML treated with intensive chemotherapy (n=[redacted])
- Compared to [redacted] patients in phase 2 study (16-10) using propensity scoring

[redacted]

[redacted]

ERG comments on company's additional evidence (1)

1
- Does not resolve uncertainty arising from lack of older patients in RATIFY

2
- Graphs are from unrelated cohorts - ≤ 60 years from UK, > 60 from US
- Linch et al. cohort divided by % of FLT ITD3 expression
- ERG interpretation – comparing highest expression group of younger patients with older patients – does not support company's conclusion that there is no change in disease risk based on age alone. Rates of overall survival are lower in the >60 cohort.

3
- ERG agrees that age is no longer the only factor for eligibility in chemotherapy, so questions why patients >60 excluded in RATIFY

4
- Cohort expanded 2 years after study began - unclear how long later-recruited patients were followed up for, or how many events they had
- ERG unsure significance of dose reduction in expanded cohort
- No patients over 70 in expanded cohort

ERG comments on company's additional evidence (2)

5

- Phase 2 study: patients could receive midostaurin after stem cell transplant – not permitted in RATIFY
- Patient characteristics not provided, but no patients over 70
- Observational study so subject to bias
- Unclear if analysis of overall survival censored for stem cell transplant
- ERG stated it could only check 2 of the 5 historical trials as no citation provided for other 3*
- Information about the 2 studies suggests historical controls may not be representative of current clinical practice e.g. treatment regimen different to RATIFY trial
- Results of comparison are more favourable to midostaurin than the results of RATIFY – appears to be due to poorer survival in historical cohort compared with control group in RATIFY

*amended after committee meeting

Key issues – clinical effectiveness

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- Is the population in the trial relevant to clinical practice in the NHS?
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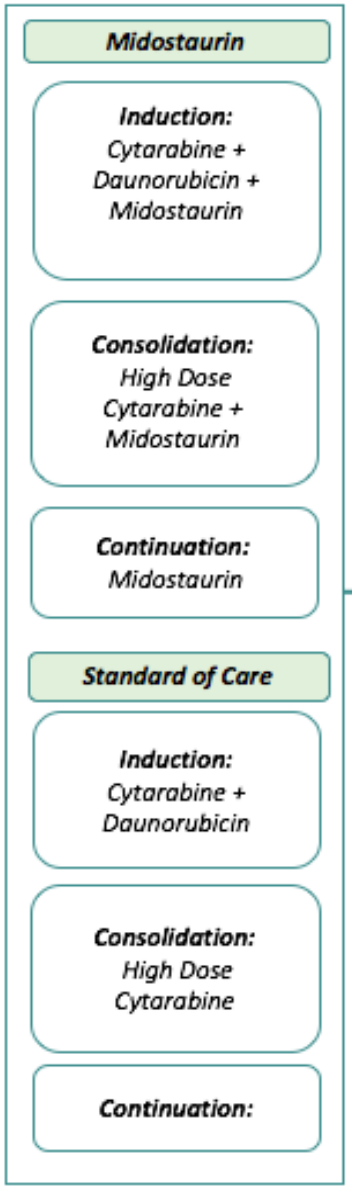
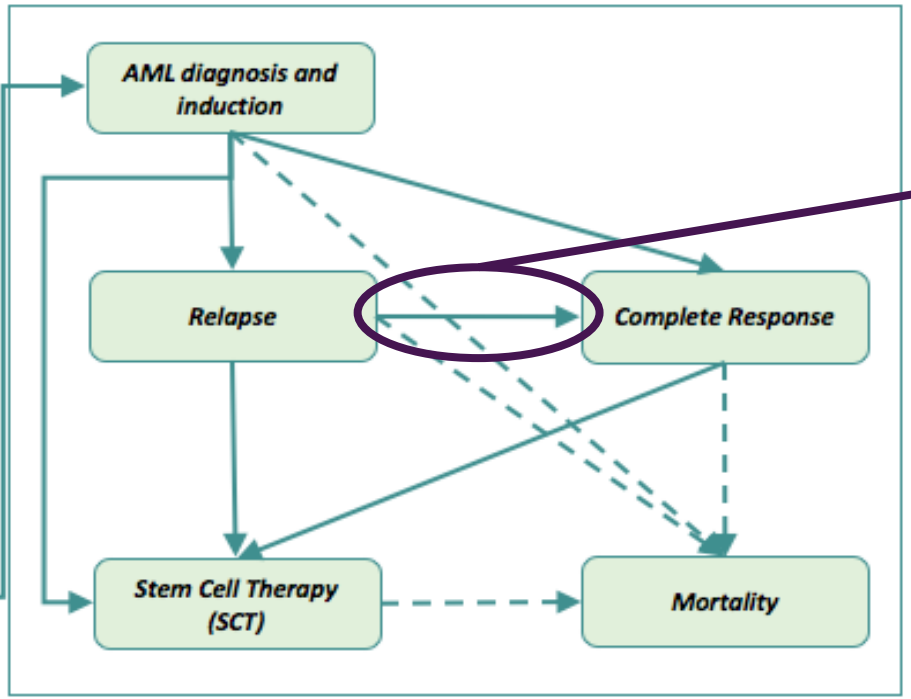
9 November 2017

Key issues

- Is the model structure appropriate?
  - What is the most plausible cure point?
  - What increase in mortality risk should be assumed after the cure point for patients with AML compared to the general population?
  - Are the OS and EFS extrapolations clinically plausible?
  - Should response to subsequent therapy (including stem cell transplant) be incorporated into the model?
  - What long-term routine care costs should be included in the CR-1L and stem cell transplant recovery health states?
  - Should utility values be adjusted for age and/or adverse effects of stem cell transplant?
- Would maintenance midostaurin be stopped at 12 months in NHS practice?
- Is it appropriate to extrapolate the cost-effectiveness results to an older population?
- Are the end-of-life criteria met?
- Is midostaurin innovative?

Company's economic model





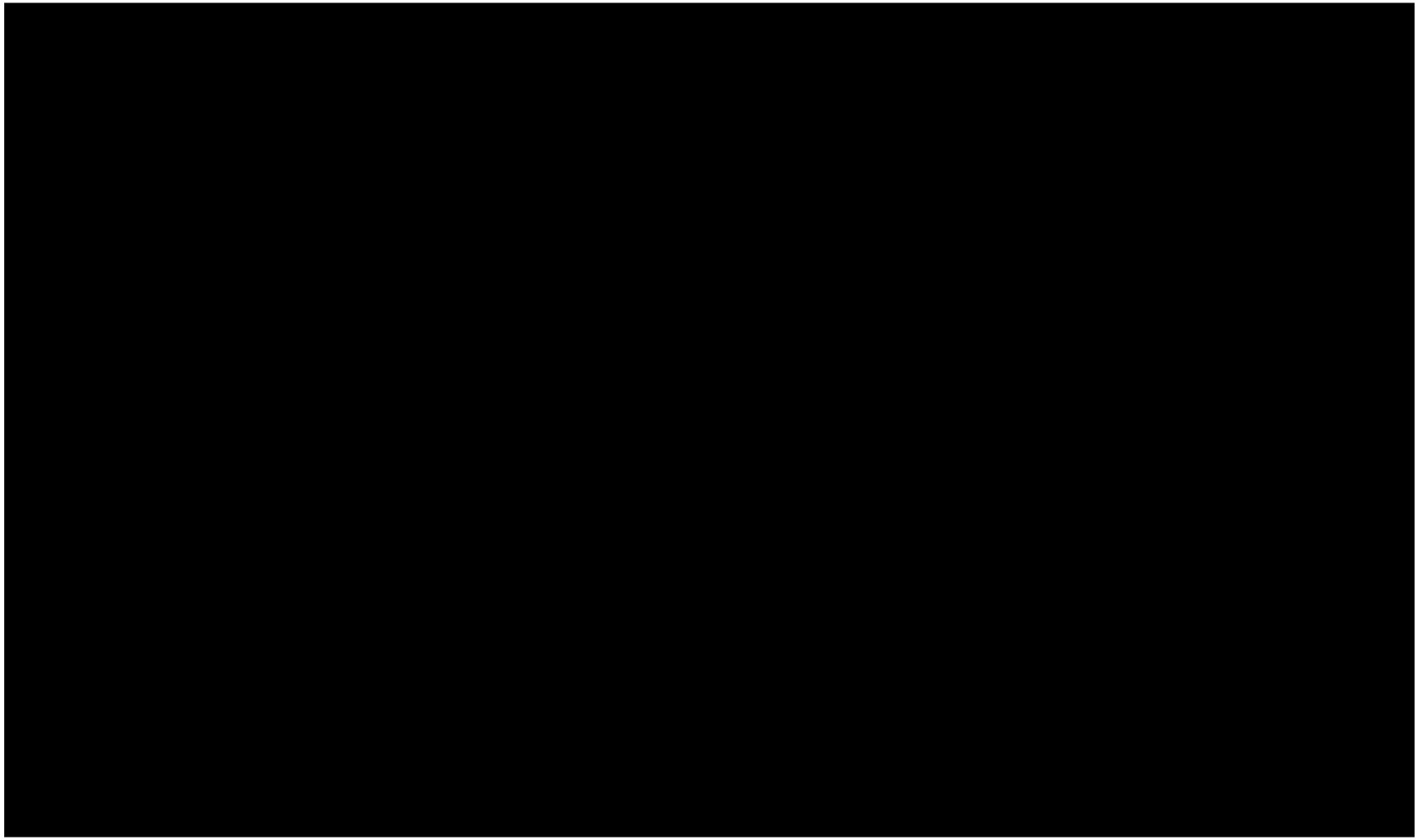
ERG comment: This transition does not happen in the model

- Partitioned survival approach
- Based on data from intention-to-treat population of RATIFY trial
- Relative dose intensities and wastage included for midostaurin, cytarabine and daunorubicin
- Equivalent lifetime horizon

Overall survival extrapolation

- Cure model used in base case, assuming rate of death of general population after trial end (approx. 6.2 years), using mortality data from Office for National Statistics adjusted for age and sex

Event-free survival extrapolation
Weibull distribution



Company's model inputs (1)
Health-related quality of life

- Health-related quality of life data not collected in RATIFY so values from literature used in economic model

Utility state	Values used in base case (literature)	Values used in scenario analysis (TTO)	Source (literature values)
Induction treatment*	0.648	[redacted]	Uyl-de Groot _Br J Haematol_1998
Consolidation treatment*	0.710	[redacted]	Batty et al 2014
Monotherapy treatment*	0.810	[redacted]	Batty et al 2014
Complete remission post-first line (no relapse)	0.830	[redacted]	Leunis et al 2014
Relapse	0.530	[redacted]	Pan et al 2010

*Includes treatment disutility
TTO, time trade off

Company's model inputs (2)

Health-related quality of life

Utility state	Values used in base case (literature)	Values used in scenario analysis (TTO)	Source (literature values)
SCT Treatment *	0.613	[redacted]	Source for Algorithm - Crott et al 2010; Source of QLQC30 data – Grulke et al 2012
SCT Recovery	0.810	[redacted]	Source for Algorithm - Crott et al 2010; Source of QLQC30 data – Grulke et al 2012
Post-SCT Recovery	0.826	[redacted]	Source for Algorithm - Crott et al 2010; Source of QLQC30 data – Grulke et al 2012

*Includes treatment disutility

TTO, time trade off; SCT, stem cell transplantation

Costs and resource use

Cost	Source
Midostaurin	Data on file
Cytarabine Daunorubicin Secondary therapy	British National Formulary https://www.bnf.org/
Stem cell therapy Routine care Adverse events	National Schedule of Reference Costs (2014-1015). NHS Trusts and NHS Foundation Trusts
Mortality	Georghiou, Theo, and Martin Bardsley. "Exploring the cost of care at the end of life." Report, Nuffield Trust, London (2014).

- Routine care use based on data used in TA399 azacitidine – includes administration costs for chemotherapies
- Patients could receive subsequent therapy (FLAG-IDA - clinical expert opinion) after primary therapy only if they had an event (including relapse or no complete remission) not related to mortality
  - Includes drug cost and routine care cost

Company's base-case results

- Taken from updated model in company's response to clarification

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of care	[redacted]	[redacted]	-	-	-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£33,672

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

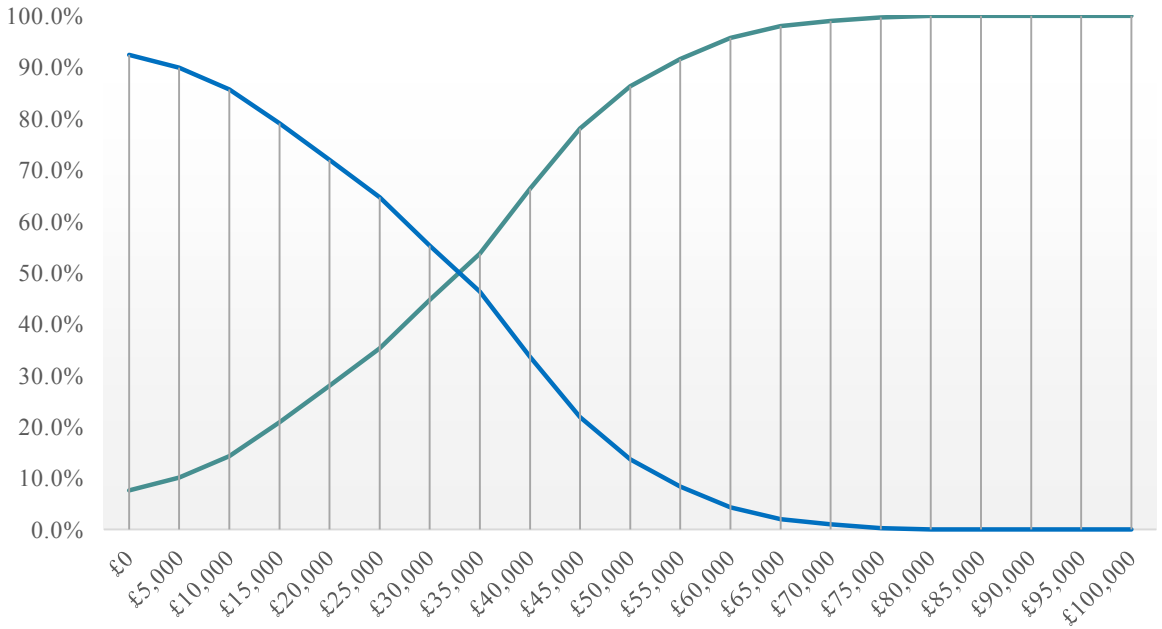
Costs included in the model

Costs in base case	Midostaurin	Standard of care	Difference
Induction	[redacted]	[redacted]	[redacted]
Consolidation	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]
Secondary therapy	[redacted]	[redacted]	[redacted]
Adverse events induction	[redacted]	[redacted]	[redacted]
AE consolidation	[redacted]	[redacted]	[redacted]
AE maintenance	[redacted]	[redacted]	[redacted]
Routine care costs during treatment	[redacted]	[redacted]	[redacted]
Routine care costs after drug treatment	[redacted]	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Company's probabilistic sensitivity analysis

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of care (SOC)	[redacted]	[redacted]	-	-	-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£33,273* (-£5,780 to £58,254)

Cost-effectiveness acceptability curve



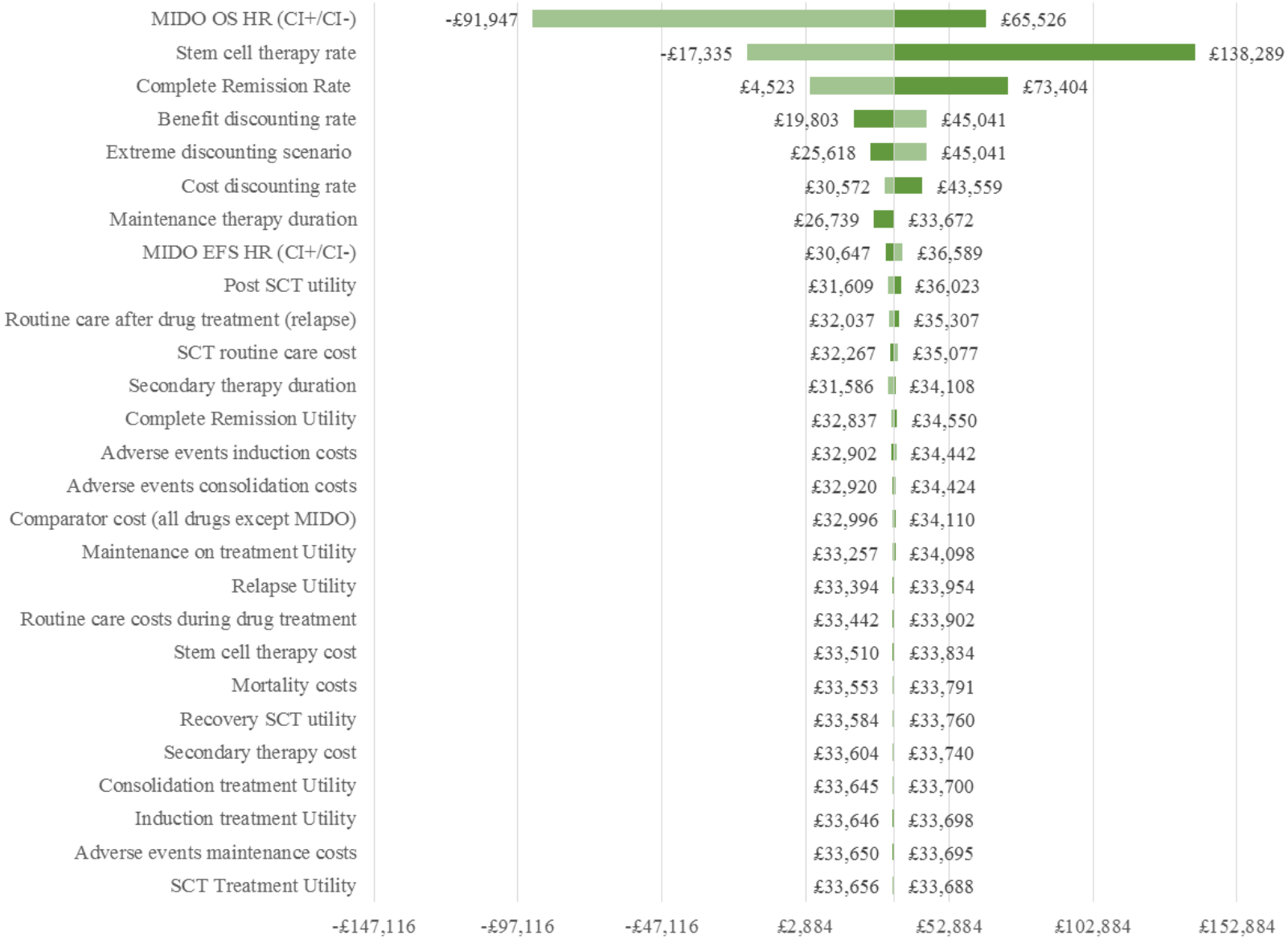
% Cost-effectiveness of midostaurin therapy

% Cost-effectiveness of SOC

Cost-effective at £30,000/QALY: **42.7%**
Cost-effective at £50,000/QALY: **86.3%**

*corrected after committee meeting

Company's deterministic sensitivity analysis



ERG's adjustments to company's base-case model

- ERG used later datacut from RATIFY as increase in patients observed at later part of Kaplan-Meier curve reduces uncertainty at base-case cure point, where overall survival differences are estimated
- Updated company model included new complete response data censored for SCT events – lacks face validity so ERG revert to original, uncensored complete response data

	ICER
Company's base case (response to clarification)	**£33,672**
1. Correction of errors and inconsistencies	£28,270
2. Use of 2016 data cut of RATIFY	£25,137
3. Use of original complete response data	£31,531
1, 2 and 3	**£28,465**

ERG's exploratory analyses

1a. Model structure - response to subsequent therapy

- Model doesn't accommodate response to subsequent therapy – patients remain in relapse state
- Sustained low health-related quality of life and high health care costs over a long time period
- ERG add new cured health state, where patients accrue same costs and QALYs as in CR 1L health state
- Scenario 3 used in ERG base case – see next slide

Scenario	Midostaurin vs standard of care		
	Inc. cost	Inc. QALY	ICER
Company base case* (corrected)	[redacted]	[redacted]	£28,465
1. Addition of cured health state	[redacted]	[redacted]	£30,821
2. Enter cured health state after 3 years	[redacted]	[redacted]	£36,555
3. Enter cured health state after discontinuing first-line treatment	[redacted]	[redacted]	£49,720

*All ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; QALY, quality adjusted life year

ERG exploratory analyses

1b. Model structure - ongoing costs in CR 1L and post-stem cell transplant

- Health states CR 1L and SCT recovery are associated with ongoing costs of approximately £8,000 per annum
- ERG considers costs unjustified and inconsistent with previous TAs
- Company's response to clarification included scenario where routine care costs reduced by 50% after 26 cycles
- Scenario 3 used in ERG base case

Scenario	Midostaurin vs SOC		
	Inc. cost	Inc. QALY	ICER
Company base case* (corrected)	[redacted]	[redacted]	£28,465
1. Zero costs after cure point	[redacted]	[redacted]	£21,201
2. Zero costs after 3 years	[redacted]	[redacted]	£19,263
3. Zero costs after discontinuing first-line treatment	[redacted]	[redacted]	£16,772
ERG preferred model structure – both scenario 3s combined	[redacted]	[redacted]	**£39,720**

*All ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; QALY, quality adjusted life year; SOC, standard of care

ERG's exploratory analyses
2. Cure assumption

- Surviving patients assumed to be cured after cycle 80
- General population mortality rates applied after cure point
- ERG considers assumption is uncertain – studies have reported higher mortality rates than general population for survivors of acute myeloid leukaemia
- 4-fold increased risk used in ERG base case (most conservative)

Scenario	Midostaurin vs SOC		
	Inc. cost	Inc. QALY	ICER
Company base case* (corrected)	[redacted]	[redacted]	£28,465
4-fold increase in mortality risk	[redacted]	[redacted]	£28,899
9-fold increase in mortality risk	[redacted]	[redacted]	£29,205

*All ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; QALY, quality adjusted life year; SOC, standard of care

ERG's exploratory analyses
3 and 4. Duration of treatment

- 3. Maximum number of cycles of monotherapy in model is 12, as in draft SPC for midostaurin – in RATIFY trial patients received up to 18 cycles
- 4. Total units of treatment received changed when model updated at clarification stage – ERG unsure why or which is correct, so explored impact of revisions in exploratory analysis

Scenario	Midostaurin vs SOC		
	Inc. cost	Inc. QALY	ICER
Company base case* (corrected)	[redacted]	[redacted]	£28,465
Up to 18 cycles of monotherapy permitted	[redacted]	[redacted]	£28,569
Reverting to original total units of treatment	[redacted]	[redacted]	£30,904

*All ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; QALY, quality adjusted life year; SOC, standard of care

ERG's exploratory analyses
5 and 6. Utility values

- 5. Utilities in CR 1L and post-stem cell transplant (SCT) recovery states were not adjusted for age – health-related quality of life in general population naturally declines with age
- 6. Disutilities and costs for adverse effect of SCT (graft versus host disease) were not included

Scenario	Midostaurin vs SOC		
	Inc. cost	Inc. QALY	ICER
Company base case* (corrected)	[redacted]	[redacted]	£28,465
Age-adjusted utilities applied	[redacted]	[redacted]	£30,354
Adverse effects of SCT applied	[redacted]	[redacted]	£30,869

*All ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio; Inc. incremental; QALY, quality adjusted life year; SOC, standard of care

Summary of ERG's exploratory analyses and base case

Amendment	ICER	Cumulative ICER
Company's base case (response to clarification) - corrected by ERG	**£28,465**	**£28,465**
1. Using ERG's preferred model structure (new cured state on discontinuing first-line treatment, zero health state costs in CR 1L and post-SCT recovery states)	£39,720	£39,720
3. Maximum number of cycles of monotherapy increased to 18 (based on RATIFY)	£28,569	£39,835
5. Age-adjusted utilities applied	£30,354	£42,734
4. Units of treatment received based on company's original model (discrepancy corrected)	£30,904	£45,937
6. Adverse events associated with SCT applied	£30,869	£49,778
2. Applying 4 fold risk to general population mortality	£28,899	£62,810
1 to 6: ERG's base case	**£62,810**	**£62,810**

Table corrected after committee meeting

ERG's exploratory analyses applied to ERG's preferred model structure

Amendment	ICER
Company's base case (response to clarification) - corrected by ERG	**£28,465**
Amendment 1. Using ERG's preferred model structure (new cured state on discontinuing first-line treatment, zero health state costs in CR 1L and post-SCT recovery states)	£39,720
Amendment 1 **and** 2. Applying 4 fold risk to general population mortality	£51,163
Amendment 1 **and** 3. Maximum number of cycles of monotherapy increased to 18 (based on RATIFY)	£39,835
Amendment 1 **and** 4. Units of treatment received based on company's original model (discrepancy corrected)	£42,694
Amendment 1 **and** 5. Age-adjusted utilities applied	£42,611
Amendment 1 **and** 6. Adverse events associated with SCT applied	£43,107
1 to 6: ERG's base case	**£62,810**

Table corrected after committee meeting

ERG further comments on cost effectiveness model (1)

Issue	Comments
Relapse after stem cell transplant (SCT)	• Literature suggests 25-40% of patients experience relapse after SCT – not possible in model • Resulting lower health-related quality of life and health care and drug costs not taken into account in model • Lack of data so issue cannot be explored further
Rate of stem cell transplant	• In model, higher rate of SCT in midostaurin group attributed only to primary therapy – leads to additional QALYs due to improved prognosis after SCT • Not clear in RATIFY that midostaurin increases rate of SCT so in practice, the increase in OS benefits may not be realised if due to SCT rather than midostaurin • Due to model structure, issue cannot be explored further
Extrapolation of complete remission	• Weibull distribution fitted to tail of Kaplan-Meier curve • ERG finds problematic, but considers extrapolation unnecessary if assuming cure after 80 cycles • Issue not explored further

ERG further comments on cost effectiveness model (2)

Issue	Comments
Mortality beyond trial follow up	• Choice of cure point important as survival gains at this point are extrapolated over lifetime • ERG explores alternative cure points (see next slide)
Utility values	• Company did not justify why sources of utility values were chosen when other sources were available • ERG explores alternative sources (see next slide)
Population	• Population in RATIFY may be younger than population eligible for midostaurin in practice • Company's scenario analysis not accepted by ERG – assumption that complete remission, stem cell transplant and overall survival before cycle 80 would be same for younger and older patients is not justified by data • ERG presents additional scenario analysis (next slide)

ERG's base case - further exploratory analyses

Amendment	ICER
ERG's preferred base case	**£62,810**
Alternative cure point	
• At 4 years	£70,160
• At 5 years	£64,207
• At 7 years	£84,161
Alternative assumptions of utility values for CR 1L and SCT post-recovery health states	
• Kurosawa 2014 (pessimistic assumption)	£66,429
• Novartis time trade off study (optimistic assumption)	£53,718
Mean age of population on entry to trial (base case 45 years)	
• 50 years	£70,513
• 55 years	£80,325
• 60 years	£92,619

Company's additional evidence: presented after ERG report received

Age adjustment in model

6a

- Younger population: Overall survival data based on intention-to-treat population from RATIFY, using initial cure model
- Older population: Overall survival data from historical comparison, extrapolated with cure model – average age at baseline considered to be 65 (45 used in initial model)

Pooled Kaplan-Meier:

- Weight of 59% applied to older population
- Weight of 41% applied to younger population

6b Model adjusted to assume mean age of patients receiving midostaurin is 65

Company's additional evidence: presented after ERG report received

6

New base case

	ICER
Previous base-case ICER (Clarification response)	**£33,672**
Using initial complete response data (uncensored for stem cell transplant)*	£18,712
Total unit of treatment as in original submission*	£19,820
Include graft versus host disease complications from stem cell transplant‡*	£21,548
Stem cell transplant costs from NHS blood and transplant 2014‡	£17,398
Routine care costs: 50% reduction after 26 cycles‡	£25,503
Updated overall survival data cut (extracted using digitalisation)*	£13,588
Age-related adjustment (based on new historical comparison) **- company's new base case including all adjustments**	**£27,754**

*Assumption consistent with ERG base case
‡Previously a company scenario analysis

ERG comments on company's revised base case

Model changes	• ERG unsure why company has adopted some changes from ERG base case and not others, and why some previous scenario analyses are now incorporated in the base case
	  • ERG's corrections of calculation error not included
	  • NHS blood and transplant used for stem cell transplant costs, although company previously stated preference for NHS reference costs – ERG agreed and used NHS reference costs in base case

Age adjustment	• Response/relapse, rate of stem cell transplant and time on treatment likely to be different between younger and older patients – only overall survival adjusted for → significant uncertainty in results of analysis • Proportion of older patients based on incidence of AML in patients over 60 – likely to overestimate proportion of older patients who would be eligible for treatment with midostaurin • Mean age of cohort used to determine mortality of patients after cure point – company assume mean age is 65. ERG estimates mean age is 56.8 → reducing mean age reduces ICER

Overall: likely that new OS data in the model overestimates benefits of midostaurin

Incorporating company's age adjustment into ERG base case

- When age adjustment made to company's base case, ICER increases
- In ERG base case, ICER decreases

	Midostaurin vs standard of care		
Scenarios	Inc. cost	Inc. QALY	ICER
Company revised base case without age related adjustment	[redacted]	[redacted]	£13,588
Company revised base case (with age related adjustment: mean age 57)	[redacted]	[redacted]	£24,001
Company revised base case (with age related adjustment: mean age 65)	[redacted]	[redacted]	**£27,754**
ERG's preferred base case (without age related adjustment)	[redacted]	[redacted]	£62,810
ERG's preferred base case (with new adjustment: mean age 57)	[redacted]	[redacted]	£35,999
ERG's preferred base case (with new adjustment: mean age 65)	[redacted]	[redacted]	£45,060

End of life considerations

Criterion	Data source	Indication	Age	Overall survival	
				Median (months)	Mean (months)
Short life expectancy, normally < 24 months	Maynadie (2013)	AML	15-70+	9.1	18
	Recher (2014)	AML	15-60	33	45
	Ohtake (2011)	AML	15-64	53	46
	Mandelli (2009)	AML	15-60	17	41
	Stone (2015) - RATIFY April 2015 cut off	FLT3+ve AML	18-60	26	[redacted]
	Company submission - RATIFY Sept 2016 cut off	FLT3+ve AML	18-60	[redacted]	[redacted]
Extension to life, normally of a mean value of ≥ 3 months				Increase with midostaurin (months)	
				Median	Mean
	RATIFY trial			49	[redacted]

ERG question relevance of Maynadie (2013) as data from 1995-2002 cancer registry.
ERG reconstructed individual patient-level data using Kaplan-Meier graphs (except median overall survival in RATIFY trial) so figures may not be exact.

Innovation and equality

- Company considers midostaurin to be innovative:
  - Induction therapy for FLT3-positive AML has not changed substantially in past 30 years
  - First targeted TKI for newly-diagnosed FLT3-positive AML
  - Inhibiting FLT3 activity is innovative
  - Offers a bridge to stem cell transplant
  - Oral therapy, no additional hospital visits

- Trial only recruited people up to age 60. Potential equality issue to consider.
  - NICE will appraise midostaurin in line with the marketing authorisation, which does not have restrictions by age. Any recommendations will not make it more difficult to access midostaurin based on age compared with other groups.

Key issues – cost effectiveness

- Is the model structure appropriate?
  - What is the most plausible cure point?
  - What increase in mortality risk should be assumed after the cure point for patients with AML compared to the general population?
  - Are the OS and EFS extrapolations clinically plausible?
  - Should response to subsequent therapy (including stem cell transplant) be incorporated into the model?
  - What long-term routine care costs should be included in the CR-1L and stem cell transplant recovery health states?
  - Should utility values be adjusted for age and/or adverse effects of stem cell transplant?
- Would maintenance midostaurin be stopped at 12 months in NHS practice?
- Is it appropriate to extrapolate the cost-effectiveness results to an older population?
- Are the end-of-life criteria met?
- Is midostaurin innovative?

Key issues – clinical effectiveness

- Is the treatment schedule used in RATIFY representative of clinical practice in the NHS?
- Is the population in the trial relevant to clinical practice in the NHS?
- Will midostaurin be used for older patients (over 60 / over 70)?
- Is midostaurin clinically effective?
- Are the adverse effects of midostaurin acceptable compared with standard of care?
- Is there uncertainty in the results because subsequent therapies were not recorded in the trial (including subsequent chemotherapy and stem cell transplant data)?
- Does the company's phase II trial provide evidence that midostaurin is effective across different age groups?